An Investigation into the Etiology of Phthisis.

BY

HENEAGE GIBBES, M. D.,
Professor of Pathology in the University of Michigan;

AND

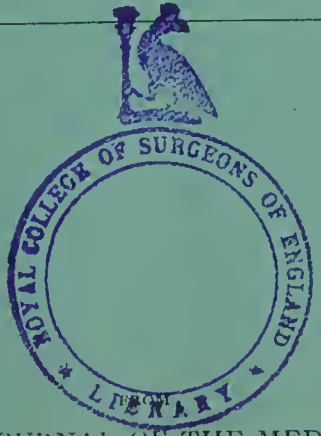
E. L. SHURLY, M. D.,
Professor of Laryngology and Clinical Medicine in the Detroit College of Medicine.

II.

On the Clinical History of Phthisis Pulmonalis.

BY

E. L. SHURLY, M. D.



THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES,
MAY, 1890.

Extracted from
The American Journal of the Medical Sciences for May, 1890.

AN INVESTIGATION INTO THE ETIOLOGY OF PHTHISIS.

By Heneage Gibbes, M.D.,
PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF MICHIGAN;

AND

E. L. Shurly, M.D.,
PROFESSOR OF LARYNGOLOGY AND CLINICAL MEDICINE IN THE DETROIT COLLEGE OF MEDICINE.

II.

On the Clinical History of Phthisis Pulmonalis.

By E. L. Shurly, M.D.

To present the following remarks upon the clinical history of phthisis pulmonalis, without reference to its etiology, would seem to be a disregard of established notions of order. But, as the subject of etiology involves pathology, and as the pathology has not yet been entirely presented by my colleague (Dr. Gibbes), it is deemed proper to leave all etiological considerations to a future time. A typical classification of the subject upon a purely clinical basis, of course, is well-nigh impossible, since a given group of symptoms or signs will embrace two or more commonly recognized varieties. I shall, therefore, present the following classification, having in mind the course only: 1st, acute; 2d, subacute; and 3d, chronic phthisis pulmonalis, leaving out of the category so-called miliary tuberculosis, which, for reasons afterward to be given, seems to be a disease of the lungs coincidently only with other organs; although, as we are aware, generally embraced under the title of pulmonary tuberculosis.

Acute Phthisis Pulmonalis, like the other classes indicated, has its period of accession, its symptomatology, and its physical signs, all of which are, in the majority of cases, quite similar to each other. The stage of accession involves antecedent injury or disease, such as an essential fever, dysentery, syphilis, rheumatism, previous acute pulmonary or bronchial attacks, etc., congenital defects of structure or function, bad habits or food, unsalubrious surroundings, over-work, over-worry, or other abnormal demands upon the economy. The symptomatology, in the rough, presents about the same features as the other varieties, except in the order or intensity of occurrence. It includes cough and expectoration, hæmoptysis, pyrexia, with rapid and small pulse, anorexia, indi-

gestion, constipation (sometimes diarrhœa), emaciation, diaphoresis, mental irritability or delirium; hoarseness and other laryngeal symptoms, ischio-rectal abscess, etc. The course is a short one, usually from two to six months, and each successive step is marked by persistent intensity. The physical signs at first are obscure; the early dyspnœa, or increased movement of chest, is frequently in part due to pyrexia; percussion may show no change (relatively) of resonance. Auscultation will, however, show diminished vesicular, and often interrupted, murmur, prolonged expiratory murmur—perhaps in patches—with abnormal transmission of heart sounds.

Soon, however, clicks, creaking, and fine moist râles (crepitant and subcrepitant) appear, generally at the upper part of the chest (unless a previous croupous pneumonia has existed, when a lower lobe may be the seat of the advanced physical signs). The clinical history would indicate that in the majority of cases it is essentially a lobular pneumonia very generally disseminated, and not a miliary tubercnlosis, as so often classified, for the following reasons: Acute tuberculosis (of which there are two forms) is a general disease, indicated by a steady, rapid loss of vitality, with a steady pyrexia, uniformly rapid and small pulse, absence of continued rigors and exacerbations and remissions; in other words, not typically hectic. There is little or no cough (unless latterly, when the lungs may be invaded); tenderness of the abdomen is a constant symptom, either of the anterior surface or of either hypochondrial region; diarrhœa is an early and more or less continuous symptom, and delirium more or less active is exceedingly common. Besides, the physical signs of the chest are almost absent, excepting, perhaps, dyspnœa, which, in this event, as before mentioned, may be very properly ascribed to pyrexia. Of course, if the patient lives long enough for the lungs to become invaded, there will be observed the usual physical signs (clicks, creaking, and moist râles) with dulness on percussion, etc. In monkeys inoculated with tuberculous sputum cough may be absent throughout the whole course, while in monkeys who contract phthisis (broncho-pneumonia) in the ordinary way (excepting by forced inhalation of dried sputum) cough is an early and persistent symptom.

The morbid anatomy also coincides with this observation, for, in the former, even at the end of two months (if they live that long), the lungs are scarcely invaded, while the spleen, liver, and other glandular organs are everywhere studded with caseous masses in various stages of degeneration. In the latter, on the other hand, the lungs are the principal seat of disease, showing more or less caseation and excavation, according to the stage of the disease (just as is observed in human phthisis), with little or no change in the other organs. Should life continue to an unusual extent, however, the disease may extend to some of the other organs. Again, acute miliary tuberculosis is not preceded by previous

pulmonary disease; in fact, as is well known, may not be recognized until the time of autopsy, while acute phthisis shows itself primarily in the pulmonary apparatus. This leads us to the consideration of another point, viz.: Whether we may not be able to recognize *clinically* two forms of miliary tuberculosis, especially in children. The one more acute, presenting all the symptoms of typhoid fever (perhaps somewhat anomalous), great adynamia, early delirium and pyrexia, abdominal tenderness with more or less diarrhœa, etc., running a course which is not typical, and showing an anomalous range of temperature. Such cases are by the most careful practitioners often diagnosed as either typhoid fever or peritonitis, until the autopsy reveals the tuberculous nature of the disease. The other form I would call attention to, is slower in its course and effects; pyrexia and emaciation are steadily progressive, not, however, reaching an intense state for, perhaps, a few weeks, and then rapidly going on to caseation and blood-poisoning. These cases show a great irregularity in their symptomatology; for instance, a great degree of adynamia rapidly succeeded by incredible strength for a short time, constipation soon succeeded by obstinate diarrhœa, anorexia and coated tongue, followed by appetite and a show of digestion, mental excitement and then hebetude, and so on, the pulse and temperature, however, keeping steadily abnormal. In either class there may be little or no cough, and scarcely any physical signs denoting disease of the chest.

Without going into further detail, suffice it to say that these two varieties of disease (not infrequently met with) differ from one another mainly by the typhoid character and more rapid course of the one, and the more general symptoms, slower course, and graded progression of the other. Notwithstanding the difficulty of making accurate clinical observations in the lower animals, we have been able, in at least two cases, to observe this differentiation in monkeys.

Subacute Phthisis, embracing all varieties between the acute and chronic forms, is undoubtedly a broncho-catarrhal or plastic pneumonia, of slowly continuous or intermittent progress, more or less localized. It may be the sequence of an acute bronchitis, a lobar or lobular pneumonitis, and by successive steps may proceed from above downward, toward the alveoli; or, originating in the lobules, proceed thence outward (as I attempted to show in a paper read in Buffalo two years ago). This course—alternate latency and intensity—is not so prominent a feature as in the chronic form, but is sufficiently striking to constitute a distinction from the acute form. Subacute phthisis is often complicated with intercurrent attacks of pleuritis, frequently regarded as tubercular pleuritis, which, of course, decidedly alter the course and sometimes the pathogenesis of the case. As shown by Aufrecht, Talma, and others, it

is probably not so much the deposit of so-called tubercle, as an extension of the inflammatory process, which brings about this complication.

Patients suffering from this form of the disease have often (although not always) a bad family history, have never been robust, show defects of structural development, either general or in the chest; show a notable lack of muscular strength—incapable of much improvement; have been throughout their lives subject to "taking cold;" have suffered more or less from some form of nasal, or naso-pharyngeal catarrh, indigestion, etc. If females, have suffered from excessive lactation, or from some uterine disease. This low state of the "economy" being unfitted to withstand the viscissitudes of every-day life in a northern climate, sooner or later shows signs of permanent pulmonary disease, such as cough, hæmoptysis, pyrexia, nocturnal diaphoresis, expectoration, anorexia, emaciation, progressive exhaustion, etc., intermissions and exacerbations taking place so that the whole course may occupy from one to two years. The physical signs, obviously, are variable, at one time showing evidence of extending inflammation and softening (moist clicks, crackling, mucous râles, with patches or areas of bronchial respiration, and bronchophony). Then signs of retrogression (dry râles, etc.) until at last, cavernous, bubbling, and gurgling râles, with signs of extended consolidation, indicate the final disorganization.

The exacerbations and remissions of this form—whether depending upon exciting causes or not, and whether ushered in with hæmoptysis or not—serve to distinguish it from the acute type; while the comparatively shorter and less complete remissions plainly distinguish it from chronic phthisis. There are cases, of course, where the line of demarcation is indistinct, especially between acute and subacute. But this fact is also applicable to other diseases as well. The ultimatum of cases ending fatally is cascation, cavitation, and often tuberculosis. This latter event, however, it seems to us, in no way invalidates the belief—based upon experiments upon monkeys, and a study of the clinical history of phthisis in children—that each form is essentially an inflammatory process, and not infrequently terminates in recovery, while recovery from general or miliary tuberculosis, as far as known, is impossible.

The high degree of adynamia often observed, as compared with the limited amount of evident local disease, might be urged in favor of the tubercular origin of the disease, if it could not be shown that the pathology and clinical history of tuberculosis do not coincide with such a view. And, further, if it were not well known that many cases of phthisis pulmonalis—with considerable lung tissue involved—show a comparatively small degree of adynamia.

Chronic Phthisis Pulmonalis, as is well known, embraces a class of cases undoubtedly similar pathologically, and certainly similar clinically, to the preceding forms, excepting, perhaps, those denominated

fibroid, by Sir Andrew Clark, and a variety commonly known as mechanical, which are supposed to differ from the ordinary types on account of the adenoid and connective tissue of the lungs being the seat of the principal morbid action. Although it must be acknowledged as a fact that some such peculiarity belongs to this class of cases, yet it is a matter of common observation that a sort of fibrosis is set up by nature in defence of nearly every attack of any considerable duration, and constitutes the most important factor of remission or "a stay of proceedings."

The clinical history of chronic pulmonary phthisis, either in its longer or shorter undulatory course, is too familiar to need detailed mention here; for all the symptoms and all the physical signs observed in disease of the lungs are, or may be, present in the course of a given case. The long duration and irregular course of many of the cases of idiopathic origin are certainly one of the inexplicable puzzles which beset the practitioner very often, and would seem to alienate it from all so-called septic or blood diseases, excepting, perhaps, syphilis, which, it must be conceded, it often resembles in its clinical history.

Whatever its pathology may show, the clinical history labels chronic phthisis an inflammatory disease of successive limitations, involving, little by little, different portions and tissues of the lungs and, therefore, producing different lesions from time to time, according to the extrinsic circumstances. What part therapeutics may play in determining the length or variability of its course, cannot be laid down as yet.

Whatever part the bacillus tuberculosis may play in the pathogenesis of the several varieties or classes of pulmonary phthisis, it would appear, from a clinical standpoint, at least, that we are forced to retain the ideas of the older authorities: That phthisis pulmonalis is primarily an inflammatory process, whether subsequently tubercle or any other degeneration appear among the inflammatory products or not, and that phthisis pulmonalis and tuberculosis are really two distinct diseases.

III.

The Tubercle Bacillus.

By Heneage Gibbes, M.D.

It will be seen from the foregoing papers that our investigations have resulted, so far, in showing that phthisis pulmonalis and tuberculosis have distinct features, both clinically and histologically. It is necessary now to review the grounds on which Koch's tubercle bacillus has been so universally accepted as the virus of tuberculosis.

First, it is assumed that the method used in cultivating this organism

frees it entirely from anything which may have been removed from the lungs with the portion of tubercle first taken to make the cultivation.

Secondly, it is stated positively that the lesion produced by the inoculation of a pure culture of tubercle bacilli, produced by these methods, results in the production of tubercles identical with those found in the human lung.

With regard to the method used in cultivating the tubercle bacilli, some remarks made by Dr. Charles Creighton, in a pamphlet published by him in 1884, deserve careful attention. He says:

"It does not appear to be generally known that the method whereby Dr. Koch professes to cultivate the microörganisms of tubercle apart from the tubercular substance and apart from all other bacteria, does not fulfil the original intention of his "dry" method at all. Dr. Koch himself never acknowledges the change of intention; on the contrary, when he announces that he will apply the dry method of pure cultivation to the bacilli of tubercle he refers the reader to page 18 of his former work (*Mittheilungen aus dem Kaiserlichen Gesundheitsamte*, vol. i., Berlin, 1881) for the principle of that method, and for a statement of its practical advantages, and in the passage referred to we find the following: 'For the subsequent cultivation of the bacilli no reliance can be placed on any method that does not provide, as far as possible, for the exclusion of foreign germs, for the isolation of those which are the objects of our study from others, which it is impossible absolutely to exclude. Such separation cannot be effected in liquid media, and we must have recourse to solids, on which each germ reproduces itself at the point where it was originally deposited.' When Dr. Koch in the opening sentences of section II of his work on tubercle (*Mittheil. aus dem K. Gesundheitsamte*, vol. ii., 1884, pp. 46–47) announces that he will adopt the dry method of cultivation as being the best, he does not discuss its suitability to the peculiar circumstances of bacilli *deeply involved in the midst of tuberculous tissue;* he merely refers his readers to a passage which is irrelevant to the question in hand, however interesting it may be in itself; and he then proceeds to apply a sort of dry method, not to separate what he calls 'strange' or 'foreign' bacteria from the rod-shaped organisms of tubercle, but to eliminate the tuberculous matter itself."

Dr. Creighton quotes from the *Medical Times and Gazette*, July 15, 1882, an article on the "Cultivation of Organisms on Dry Surfaces:"

"He [Dr. Koch] started, indeed, with the same intention, viz., to separate the bacilli of tubercle from other bacilli that may have been mixed with them. But that purpose very soon became subordinated to another and more arduous task—the separation of the tuberculous matter from the organisms present in it. So absorbing did the new factor in the problem prove to be that he disregarded altogether his original purpose of separating one kind of bacillus from another; if anything led him to suspect that the bacilli of putrefaction were present, he did not attempt to eliminate them, but he discarded that particular test-tube altogether. Thus, the dry method, which had certain recommendations for one particular purpose, came in the course of the research to be used for another and quite different purpose, for which it had nothing originally to recommend it. The task of separating various kinds of bacilli from one another being given up, no one would choose the method of cultivating on a dry surface in preference to cultivating in fluid, if his intention was to show that he had completely eliminated the presence of virulent tubercular matter. . . . Dr. Koch nowhere professes to use the fractional method. I can find only one passage in the whole of his monograph (p. 52) in which he tells us how much of the dried-up matter he took from the first test-tube to transfer to the second; and in that passage he merely says 'einige

schüppchen.' It appears to me that this is the crux of the whole cultivation experiment, and Dr. Koch passes it over almost in silence. . . . It is in vain for Dr. Koch and Mr. Cheyne to assure us that the dried-up matter which they scraped together for an inoculation experiment from the serum-coated surface of the last test tube was bacilli and nothing else. No one would expect to find morphological traces of tubercle in it; the heat of an oven at 98° F. for several weeks would be sure to resolve the original pieces of tubercle to amorphous particles. But nothing is anywhere said of a residue of tubercular dust on the surface of the serum; and we are left to suppose that the detritus of the tissue entered into the composition of the crusts and scales and was transferred with them. It was not until the last cultivation was finished that Dr. Koch really pulverized them (in a mortar with a little boiling water) previous to inoculatiug them upon animals."

"That the bacilli grew and multiplied in these crusts cannot be doubted, but there is no evidence to show that the substance which emerged from the routine process was essentially different from the substance that went in."

I have quoted so much from Dr. Creighton's article, as it will show that to an impartial observer there are several points in Koch's own history of his work which are open to adverse criticism. Many other observers have traversed the same ground; notably Spina, who took up separately every claim of Koch's and produced arguments and experiments to disprove them. Instead of meeting Spina's arguments in a scientific manner, Koch made an attack on him, accusing him of ignorance in the same manner he had formerly attacked Pasteur. This method of disarming criticism has been adopted by some of Koch's disciples. Dr. Formad, in a series of articles in the *Philadelphia Medical Times*, 1884, makes some pertinent remarks on the subject. In a visit to Koch's laboratory he states that Koch had an excellent staff of assistants, but it was a matter of surprise that there was not a single competent pathologist connected with the laboratory. This remark I have heard from many who have worked in Koch's laboratory and its significance can hardly be underestimated. Dr. Formad states:

"Watson Cheyne, to whom the British Association for the Advancement of Science by Research had intrusted the investigation of tuberculosis and the testing of Koch's researches, did not do justice to his mission. From Cheyne's report (*The Practitioner*, April, 1883) it is seen that he made no earnest attempt to study the nature of tuberculosis, because all he did was to study and experiment with bacteria met with in tuberculous lesions. He went to see some of the different mycologists, consulting only believers in the germ theory; obtained some French and German bacteridian material, and, after testing the same, he reports, with great emphasis, that Koch's tubercle bacilli are the more genuine tubercular virus than Kleb's or Toussaint's micrococci. He did not inquire, nor did he care, whether tuberculosis may have any other cause! He simply imitated Koch's experiments with the bacillus material in rabbits and guinea-pigs (only),and obtained, of course, the same results. Furthermore, he made some control experiments which, as I will show, pass for naught, as they are much more deficient than those of Koch."

I have already alluded to the unreliability of Watson Cheyne's work. In spite of all this, in *Green's Pathology*, 7th ed., 1889, p. 347, Eng. ed., occurs the following:

"These results (Koch's) have been fully confirmed, especially by Cheyne (*Practitioner*, April, 1883), and there is now no doubt that they are absolutely true."

Dr. Formad's artieles extend through four numbers of the *Philadelphia Medical Times*, 1884, and they are well worth reading at the present time.

In regard to eultivations on solid media, sueh as the blood serum used by Koeh, the investigation made by Dr. Klein into the aetion of the jequirity baeillus has a most important bearing. These researches are published in the supplement to the *Thirteenth Annual Report of the Local Government Board*, London, 1883–84. In 1882 de Weeker, of Paris, drew attention to the therapeutie value of the beans of Abrus preeatorius. They are used in the Brazils under the name of jequirity in the ease of granular lids or trachoma. Sattler found that when an infusion of the beans had been made, after a time it would eontain numerous baeilli resembling bacillus subtilis. Sattler cultivated these bacilli on blood serum and gelatin through suceessive eultivations and yet he found that they retained their specifie properties. Dr. Klein made an infusion of the beans with every possible preeaution to prevent eontamination, and fifteen minutes after it was made inoeulated the eyes of healthy rabbits with it, at the same time he inoeulated a number of test-tubes eontaining sterile peptone solution, broth, etc. Intense inflammation was produeed in the rabbits' eyeballs in twenty-four hours, while all the test-tubes were elear and limpid and they remained so. No growths of miero-organisms appeared. It was shown by Sattler that the spores of these bacilli would stand boiling for a few minutes. Klein took an infusion of the beans full of baeilli and spores and boiled it for half a minute; he then inoeulated sterile test-tubes with this boiled infusion, these tubes were placed in the ineubator and kept at a temperature of 35° C.; after twenty-four to forty-eight hours the fluids were found to be teeming with the jequirity bacillus. But no amount of this material produeed the least symptoms of ophthalmia, the boiling had rendered it inert.

Drs. Warden and Waddell, of Calcutta, had, however, prior to Klein's experiment, isolated an amorphous solid which they named "Abrin." This was the poisonous prineiple of the beans and the baeilli had no action in the matter. It is obvious from this that some portion of the chemieal poison had been carried over in eaeh suceessive eultivation in the solid eulture-medium. Can we say that Koeh's experiments are free from the same fault? A number of experiments have been made from time to time by independent observers, whieh have caused them to express grave doubts as to the exaet relation of the tuberele baeillus to phthisis.

THE NATURE OF THE LESION PRODUCED BY THE INOCULATION OF TUBERCULOUS MATTER IN ANIMALS.

I have already stated in my former paper that the artificial tubercle produced by the inoculation of human tubercular material in the lower animals in no wise resembles the typical human tubercle. I mean by this the reticular form which I have fully described, which is also fully described by Dr. Payne in his work on pathology, and there stated to be the type of tuberculosis. Neither does the artificial tubercle resemble the other form or caseous tubercle already mentioned. The small, rounded nodules which form in the lungs and other organs of inoculated animals in few cases contain any giant cells, and when they are present they do not in the least resemble those found in the human lungs; they are exactly similar to those described by Zeigler in his researches with glass plates inserted into the tissues of animals; they also resemble those occasionally found in inflammatory tissue. It must be evident to every careful observer that the giant cells in the human lungs are not, as it were, accidental formations. From their similarity and from the arrangement of their nuclei they must all have been formed in a somewhat similar manner. It seems to me probable that they originate in the lungs from a fusion of the cells in the infundibula and alveolar ducts; their arrangement round the periphery of the cell, and the evident tubular appearance presented by some, which can be well seen with a binocular microscope, certainly favor this view, but this will not account for their formation in lymph glands. In tubercle of the testis, I have before now demonstrated the process of their formation from the fusion of the epithelium in the seminiferous tubes. Now, no one, I imagine, pretends to say that giant cells of this kind occur in artificial tubercle of the lungs. Next, the reticular stroma so well marked in the reticular tubercle of the human lung, is never seen.

Here, then, are two of the essential features of typical human tubercle which are absent from the artificial in lower animals. Where, then, is the resemblance?

In artificial tuberculosis there is an aggregation of round cells; this forms a nodule, which in the early stage is of a rounded form.

Careful examination shows this to consist of cells which vary in shape and size, but which in many cases are larger than a red-blood corpuscle, while a few assume large proportions and contain several nuclei. This is evidently some process of a subacute character induced by the inoculated material which acts on the normal cells, causing swelling and slow disintegration. To understand this process, it is necessary to examine sections from lungs or other organs where it is just commencing. For this it will be found advisable to inoculate several animals and kill them at varying periods, from ten days to a month or more. One of the best

examples I have ever seen was in a monkey, which I inoculated with human sputum from a typical case of rapid phthisis; this animal died from accident twenty-two days afterward, and the only abnormal change was in the spleen. Some of the Malpighian corpuscles with a low power showed a small round mass in or about the centre, which had not taken the logwood stain in the same manner as the other parts. On examining these with a higher magnification they were found to consist of cells which were evidently those of the normal adenoid tissue, but under some abnormal influence. On examining the small arteries in the Malpighian corpuscles they showed a thickening of their walls and obliteration of some of the muscle coat from the infiltration of a hyaline material. In some places this projected beyond the wall of the vessel. The appearances presented by these small arteries were somewhat similar to those seen in scarlatinal nephritis. Among the altered cells was also a quantity of hyaline material, in which they seemed to be imbedded. This hyaline matter stained very faintly with logwood. The cells themselves presented various appearances; they had become enlarged and the majority had altered their shape, becoming elongated or angular, but some were oval; all, however, had become more transparent. and the intra-nuclear network, now showing plainly, gave them a granular appearance. There was nothing to show any inflammatory change. The process seemed to be a gradual one. This is the appearance presented by the smallest nodules when examined with a one-twelfth oil immersion and good illumination. All sections from this spleen presented the same changes.

I then examined the lungs of another monkey which had been killed six weeks after inoculation and where the morbid changes in those organs were very slight. I found precisely the same appearances. I then examined the organs of various animals, all inoculated with human phthisical material, and I found that from the initial changes already described the process went on in a similar manner until the nodules became very much larger, the cells gradually becoming paler and disintegrating, until in the older nodules a mass of amorphous material occupied the whole of the centre; some slight inflammatory action was set up in these at the periphery in some cases. There is nothing whatever in these nodules at any stage that resembles the fibroid reticulum found in a typical miliary tubercle of the human lung.

It is as well here to notice a statement made by Friedländer, as well as by Cornil and Ranvier, that this reticular structure is not present in the fresh tubercle but is due to the hardening process. This I am positive is incorrect, as I have used various hardening methods and the result is always the same—either caseous or reticular tubercle. It is not likely that different hardening methods would produce identical results if those results were due to the hardening process itself. I always use, in these

eases, strong aleohol, or Müller's fluid, and use these methods because I have to seek for the presenee of baeilli; but if, in any case I wish to study the histological features, I then harden a portion of the tissue in chromic acid mixture, which eould not be done if the bacilli had to be studied, as it prevents their staining.

I will now mention briefly the results obtained in an investigation earried on by me under the direetion of Dr. Klein, for the Local Government Board, London, in 1883–84. A large number of guinea-pigs were inoeulated with human sputum full of baeilli from eases of tuberculosis. The experiments were made in my laboratory, and at the end of the year's work I submitted my report, together with mieroseopieal slides of all the eases, to Dr. Klein. I will mention some of the eonclusions he drew from the investigation. I quote from the supplement to the *Thirteenth Annual Report of the Local Government Board:*

"From this series of experiments we learn, then, that after inoculating guinea-pigs with sputum of human tuberculous lungs full of tubercle bacilli, the animals become, in the majority of instances, afflicted with a general pathological condition consisting in enlargement and deposit of tubercles in the lymph glands, lungs, etc. . . . We seem to be yet far from understanding the share of the bacilli in the production of what we speak of pathologically as tubercles. . . . Mr. Watson Cheyne says that the tubercle bacilli first invade the epithelial cells and then set up a multiplication of these, associated with certain vascular inflammatory changes, leading to the formation of tubercles. I have before me sections through typical tubercles in all stages in the lung and liver of some of the guinea-pigs above described, and I fail to see that this statement is in any way borne out by the facts of the case. I find some tubercles in liver and lung which are in an early stage of formation and in which there is not a trace of any tubercle bacilli . . . owing to the fact that in the cascating lymph glands, near the seat of inoculation, and in the caseous or advanced tubercles, the bacilli occurred numerously, we are justified in assuming that caseous matter is a very good nidus for their multiplication. But we may not, from the facts above enumerated, infer that the presence of the bacilli starts, so to speak, the several tubercles. . . . I think that their presence in a tubercle does not necessarily mean that they preceded the tubercle; and, if this be conceded, as I think it must be conceded, it further follows that the formation of the tubercles is not a direct result of the presence of the bacilli. The next series of experiments was made on rabbits, and this is the conclusion drawn: From this we see, then, using human tubercular matter full of bacilli, no general tuberculosis was produced in rabbits; in one instance only a local effect—abscess—was produced containing bacilli; in half the instances a localized pneumonia with bacilli was established, and that was all. We have, then, a marked difference between guinea-pigs and rabbits as regards human tubercular matter."

In the following year I made a series of experiments in feeding guinea-pigs and rabbits with human tubercular matter—*Fourteenth Annual Report Local Government Board*, London. Klein says:

"On comparing the results of the above experiments with those produced by subcutaneous inoculation . . . it will be seen that the effect of feeding animals on tubercular matter differs little from that obtained by inoculation . . . in the guinea-pigs; though a general tuberculosis was produced, the process did not seem so rapid as when the tubercular matter was inoculated into the system. . . . In rabbits the morbid change was confined to the

lungs, and even in one allowed to live for over thirty-six weeks. No other organ was affected. . . . It is worthy of notice, that in rabbits, no matter whether the virus had been introduced by feeding or by inoculation, the lungs were the only organs affected. . . . The distribution of the tubercle bacilli appears to vary very much, but it has this constant feature: it is always associated with cascation. In many organs taken from animals killed in the early stages of tuberculosis—*i. e.*, at the very commencement of the process—the most careful examination of a very large number of sections failed in every instance in detecting any tubercle bacilli."

I have since this carried out a large number of experiments with monkeys in the same manner, and I have invariably found the same results. The lesions produced in the monkey are identical with those of the guinea-pig and I could produce no change in the process by inoculating from one animal to the other, and *vice versâ*. It will be seen from the above, that the tubercle bacillus—the cause of tubercular growth—is invariably absent from the first commencement of the disease-process it initiates and does not appear on the scene until the lesion it has produced has begun to decay—that is, caseate. The only way to get over this by those holding the bacillary views was to ignore it, and that is what was done. Surely, now, after these years the subject may be approached in a scientific manner and the above experiments disproved if possible. Many of the statements made contradicted themselves. Dr. Payne, in his work on *Pathology*, p. 254, under the heading "The Processes of Disease," speaking of the action of microörganisms, says:

"They do not cause overgrowths directly, but only produce the reaction growth of inflammation above described. This growth is, accordingly, limited to the connective tissue and is not essentially different from that set up by other injuries."

At page 489, in speaking of the action of tubercle bacilli in pulmonary phthisis, he says:

"Within the alveoli, and possibly in the smallest bronchioles, they set up changes resulting in the formation of a miliary tubercle. It is now clearly established that the tubercle is formed at first inside the alveoli, though at one time it was thought to belong especially to the interstitial structure of the lung."

Here is a definite statement as to the action of the bacillus, but its action is here said to be on epithelial structures, not on connective tissue, as stated before. Dr. Payne, therefore, must mean that the reticular fibroid structures, as well as the giant cells, are formed by the action of the bacillus on the walls of the alveoli of the lung, which are composed of cells of hypoblastic origin. Now, in many cases of tuberculosis where the tubercles are of the reticular form, identical tubercles are found in the lymph glands. Are we, then, to understand that the tubercle bacillus is able to form a reticular tubercle from material, no matter whether it is of hypoblastic or mesoblastic origin, and this tubercle is exactly similar in either case? At page 498 he says:

"The inoculated disease must necessarily be considered as the same since they may be derived from human tubercle, and their anatomical characters are identical."

All my experience in inoculating animals goes to disprove this statement, as I have said before; and further, the bacillus cannot be found in the earliest stage of the change it is supposed to initiate.

In the case of the monkeys before mentioned I carried out two elaborate series of experiments to try and find the tubercle bacillus in the commencing nodules, using three or four of the most approved methods of staining, and in some cases leaving the sections in the stain four or five days. These experiments were conducted with the greatest care, and yet not one single bacillus could be found with a one-twelfth oil immersion or Zeiss's apochromatic lens. Among the control experiments at the same time with the same stains, sections of lungs with tuberculosis that had been in spirit for eighteen years, gave multitudes of bacilli brightly stained, sputum kept in the open air for three months showed numerous bacilli, and sputum spread in May, 1883, on cover-glasses and kept in an ordinary pill-box, came out as brilliantly as when perfectly fresh. I think after this I am justified in considering that the bacilli could not be found, because they were not there.

If, from the time of Koch's announcement of his discovery in 1882 up to the present time, there had been series of investigations all more or less confirming it, there would be nothing at all surprising in the fact that the majority of the writers of the present day should accept it as an established fact. But that this is not the case is shown by the authors of the latest text-books in the English language quoting as their authority work done in 1882–83, which has been shown by many investigators to be unreliable.

In speaking of pulmonary phthisis Dr. Frederick T. Roberts, of University College, London, in his *Hand-book of the Theory and Practice of Medicine*, 7th ed., 1888, p. 451 (Eng. ed.), says:

"Without entering into any discussion on the subject, I must still express my concurrence with those who take a wider view of the pathology of this complaint than to regard it as being always tubercular, and still less as invariably requiring the action of tubercle bacilli for its development."

Dr. Douglas Powell, in his work on *Diseases of the Lungs*, says, page 280 (Eng. ed.), 1886:

"It cannot then be said that the position of the tubercle bacillus, with regard to the etiology of phthisis is as yet established, although so intimate and exclusive is its association with the lesions of that disease that by its recognition in excreta or expectorations, we obtain a valuable criterion for diagnosis in obscure cases."

Aufrecht, in a work recently published, says he cannot see how medical men can think and believe that the bacillary origin of tuberculosis is an established fact. He thinks the adoption of the above view has

brought confusion into the clinical side of the question. He says the outcome of his investigations leads him to think that the pathological change is not the same in all cases, the disease not running the same course clinically. This is important as coming from a man who has worked with Koch on the spot, and the book is well worth reading.

I have said enough to show that there is still room for work before this question is finally settled.

There are one or two interesting points that have occurred in my investigations which may be worth mentioning. One of these was where I inoculated three monkeys at the same time, with the same sputum, from an acute case of phthisis. Ten days after the inoculation one of the monkeys seemed to be ill and weak, although previously I could see nothing the matter with him; he was not very carefully examined, as he was savage and had awful teeth, and on the next day I chloroformed him. On making a post-mortem examination, I found that he was the subject of general tuberculosis in a most marked degree. On examining the place where I had inoculated him, I was unable to find the slightest trace of the puncture; the sputum had been absorbed without producing any inflammatory symptoms whatever. This seems to show that tuberculosis is a constitutional disease and that animals suffering from it are insusceptible to further inoculation.

The other two monkeys developed large abscesses at the seat of inoculation. When I opened the abdominal cavity of this monkey, I found a fine living specimen of pentastoma constrictum lying free in the omentum. It measured just an inch in length. I have often found them encysted in the liver of monkeys, but never before free in the abdominal cavity. Pentastoma constrictum has been found in the human liver and lungs, and this case of the monkey shows that it is possible for it to get free in the human abdominal cavity.

Another point having some bearing on the heredity of tuberculosis may be of interest. I inoculated two guinea-pigs with the same human sputum; one of these was a male and the other a pregnant female. The male died twenty days after inoculation with general tuberculosis. About a month after the inoculation the female had four young; she died five months and twenty-eight days after inoculation, of general tuberculosis. A second experiment on two females was made, in which the non-pregnant guinea-pig died thirty-five days after inoculation; the pregnant one had four young and died four months after inoculation. I kept these young guinea-pigs separate from others, and as soon as they were old enough, I bred them in and in (brother and sister), keeping each lot distinct. I did this in the one case for five generations, in the other for seven, and out of every litter I took one when half-grown and killed it, and examined all the organs. They were in every case perfectly normal.

I tried several experiments, such as placing one of a litter in a cage with two inoculated animals, and keeping it there for a week, while others were allowed to remain all the time in the house where the inoculated animals were kept; I found, however, that in these animals nothing short of actual inoculation would produce tuberculosis, and then it differed in no way from that produced in other guinea-pigs. Here there were animals notoriously prone to become tuberculous in their ordinary state, rendered doubly so, one would think, from their history and surroundings, and yet they did not become tuberculous unless the tubercular matter was actually introduced into their systems.

In my next paper I shall discuss the question of bovine tuberculosis and spontaneous tuberculosis in other animals and birds; also cases where the liver and other organs of animals, birds, and snakes contained numbers of bacilli having the distinctive reaction of tubercle bacilli, but without the formation of tubercles.